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Signed Stephen Hordley

Dated 4 June 2004

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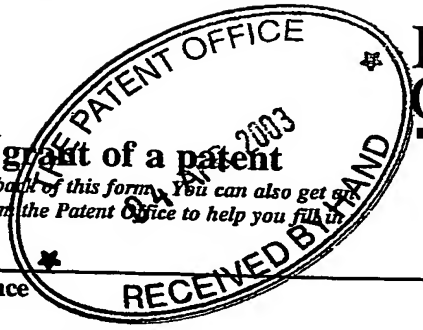

The Patent Office

1/77

Request for grant of a patent

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The Patent Office
Cardiff Road
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1. **Your reference** 444.77666/000

2. **Patent application number** *(The Patent Office will fill in this part)* 0307834.2

07APR03 E797954-3 D00027
P01/7700 0.00-0307834.2

3. **Full name, address and postcode of the or of each applicant** *(underline all surnames)*

TA Contrast AB
Lybska vägen 10
SE-23940 Falsterbo
Sweden

Patents ADP number *(if you know it)* 8604118001

If the applicant is a corporate body, give country/state of incorporation Sweden

4. **Title of the invention** COMPOSITION

5. **Name of your agent** *(if you have one)*

Frank B. Dehn & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

179 Queen Victoria Street
London
EC4V 4EL

Patents ADP number *(if you know it)* 166001

6. **If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and** *(if you know it)* **the or each application number**

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. **If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application**

Number of earlier application	Date of filing *(day / month / year)*

8. **Is a statement of inventorship and of right to grant of a patent required in support of this request?** *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

Patents Form 1/77

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Continuation sheets of this form	0
Description	27
Claim(s)	3
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Priority documents	-
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature Date 4th April 2003
Frank B Dehn & Co

12. Name and daytime telephone number of person to contact in the United Kingdom

Julian Cockbain
020 7206 0600

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77666.619

Composition

This invention relates to bone cement compositions and kits therefore and to the use of organoiodine compounds in the manufacture of bone cements.

In the elderly, in particular, it is frequently necessary to replace a skeletal joint (commonly the hip joint) with a prosthetic joint. Currently, about one million such operations are carried out annually. In the case of the hip joint, a metal pin carrying a replacement "ball" for the ball-in-socket joint is cemented into the longitudinal cavity in the femur, usually using an acrylic bone cement.

Such joint prostheses often have to be repaired or replaced, e.g. as a result of the metal pin becoming loose.

In order that the placement of the metal pin within the femur may be monitored, e.g. shortly after the operation to insert the prosthesis or over the subsequent years, it is common for the bone cement used to contain a compound with the ability to absorb X-rays, i.e. a radioopaque material such as zirconia. In general, such radioopaque materials have been compounds of heavy metals, for example incorporated into the bone cement as insoluble particles. This however has the drawbacks that the particles reduce the mechanical strength of the polymer matrix of the set cement and that any release of the radioopaque material from the surface of the cement or on failure of the cement distributes highly abrasive particles into the joint.

One solution that has been proposed has been to utilize as a monomer, in the preparation of one component of the bone cement polymer matrix, a compound comprising an iodophenyl group linked to an acrylic group via an ester group (e.g. 2-methacryloyloxyethyl (2,3,5-triiodobenzoate), 2-methacryloyloxypropyl(2,3,5-

triiodobenzoate), and 3-methacryloyloxypropyl-1,2-bis (2,3,5-triiodobenzoate) (see Davy et al. Polymer International 43:143-154 (1997)), 2,5-diiodo-8-quinolyl methacrylate (see Vazquez et al. Biomaterials 20:2047-2053 (1999)), and 4-iodophenyl methacrylate (see Kruft et al. J. Biomedical Materials Res. 28:1259-1266 (1994)). It is clear however that the resulting set cement will not only contain residual unreacted organoiodine monomer, but that exposure to physiological fluids will result in the release of organoiodine compounds with unclear physiological compatibility due to cleavage of ester bonds.

An alternative approach has been to incorporate in the bone cement particles of water-soluble X-ray contrast agents, e.g. iodixanol or iohexol (see Sabokbar et al. 46th Annual Meeting of the Orthopaedic Research Society, March 12-15, 2000, Orlando, Florida, page 0171). While avoiding the problem of the release of abrasive radioopaque particles from the bone cement, this approach however does not address the problem of impaired mechanical strength experienced with the conventional use of radioopaque particles of for example zirconia or barium sulphate.

Furthermore, neither of these approaches will produce cements in which the radioopaque material is substantially uniformly distributed in the set cement as, in order to reduce the amount of heat emitted on setting of the cement, it is conventional to use a two part cement using about 2 parts by weight of a preformed particulate polymer to about one part by weight of a liquid comprising monomer and a polymerization initiator.

We have now realized that these problems with radioopaque bone cements may be addressed by adopting one, two or three of the following strategies: firstly incorporating in the cement a non-polymerizable organoiodine compound which is soluble in the monomer

from which the polymer matrix is produced; secondly by incorporating a polymerizable organoiodine monomer (or cross-linking agent) as part of the polymer matrix both in the part formed from the liquid monomer component and in the preformed polymer particles; and thirdly by the use of a polymerizable organoiodine monomer comprising an organoiodine group coupled via amide rather than ester bonds to at least one group copolymerizable with acrylic monomers.

By polymerizable and non-polymerizable herein is meant that the compound in question can or respectively cannot participate in the polymerization reaction to become a covalently bound portion of the polymer matrix in the set bone cement.

Thus viewed from one aspect the invention provides a bone cement comprising in admixture a monomer-containing liquid portion and a particulate polymer portion, characterized in that at least one of said portions comprises a dissolved non-polymerizable organoiodine compound.

Viewed from a further aspect the invention comprises a bone cement kit comprising a monomer-containing liquid portion and separate therefrom a particulate polymer portion, wherein at least one of said portions comprises a dissolved non-polymerizable organoiodine compound, said kit optionally and preferably further comprising instructions for the preparation of a bone cement therewith.

Viewed from a still further aspect the invention provides a bone cement comprising in admixture a monomer-containing liquid portion and a particulate polymer portion, characterized in that said liquid portion comprises a polymerizable organoiodine compound and the polymeric structure of said particulate polymer comprises covalently bonded residues of a polymerizable organoiodine compound.

Viewed from another aspect the invention provides a

bone cement kit comprising a monomer-containing liquid portion and separate therefrom a particulate polymer portion, wherein said liquid portion comprises a polymerizable organoiodine compound and the polymeric structure of said particulate polymer comprises covalently bonded residues of a polymerizable organoiodine compound, said kit optionally and preferably further comprising instructions for the preparation of a bone cement therewith.

Viewed from a further aspect the invention provides a bone cement comprising in admixture a monomer-containing liquid portion and a particulate polymer portion, characterized in that said liquid portion comprises a polymerizable organoiodine compound and/or the polymeric structure of said particulate polymer comprises covalently bonded residues of a polymerizable organoiodine compound, wherein said polymerizable organoiodine compound comprises an organoiodine moiety covalently bonded via an amide but not an ester bond to a polymerizable moiety.

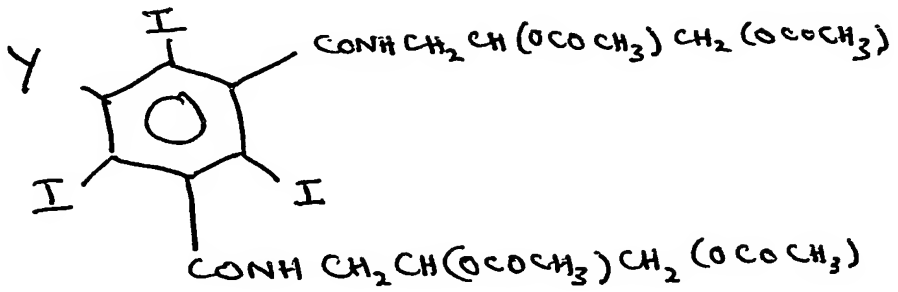
Viewed from another aspect the invention provides a bone cement kit comprising a monomer-containing liquid portion and separate therefrom a particulate polymer portion, wherein said liquid portion comprises a polymerizable organoiodine compound and/or the polymeric structure of said particulate polymer comprises covalently bonded residues of a polymerizable organoiodine compound, wherein said polymerizable organoiodine compound comprises an organoiodine moiety covalently bonded via an amide but not an ester bond to a polymerizable moiety.

The organoiodine compound(s) used in the present invention are preferably iodobenzene compounds (i.e. having iodine as a ring substituent on an aromatic C_6 ring), especially diiodo or more preferably triiodo benzene compounds, in particular diiodo and triiodo benzene compounds having the iodines at non-adjacent ring positions. The iodobenzene ring is preferably also substituted by one, two or three substituent groups comprising non-polymerizable lipophilic groups and/or polymerizable groups, preferably acrylate or methacrylate groups, and/or polymerizable or non-polymerizable groups coupled to a further iodobenzene ring (preferably a triiodobenzene ring). The non-polymerizable lipophilic groups are preferably acrylamino or alkylaminocarbonyl groups, or more preferably acyloxyalkylcarbonylamino, acyloxyalkylaminocarbonyl, alkoxyalkylaminocarbonyl or alkoxyalkylcarbonylamino groups, i.e. groups which on hydrolysis (for example due to esterases encountered in the body) will serve to solubilize the iodobenzene moiety, e.g. groups of formula

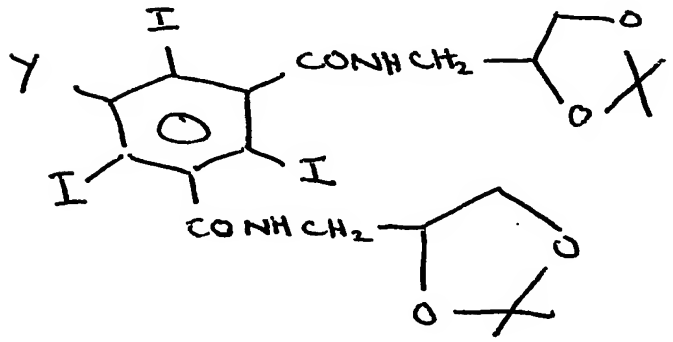
$(R^1COO)_nXCONR^2-$ or
$(R^1COO)_nXNR^2CO-$ or
$((R^1COO)_nX)_2NCO-$ or
$(R^3O)_nXCONR^2-$ or
$(R^3O)_nXNR^2CO-$ or
$((R^3O)_nX)_2NCO-$

(where n is 1, 2, 3 or 4, preferably 2 or 3;
R^1 is a C_{1-6} alkyl group, especially a methyl group;
X is a C_{1-6} alkylene group, especially an ethylene and more especially a propylene group;
R^2 is hydrogen or a C_{1-6} alkyl group, especially hydrogen or a methyl group, and R^3 is a C_{1-6} alkyl group, especially a methyl group, or two groups R^3 together form a C_{1-6} alkanediyl group, e.g. a propan-2,2-diyl group).

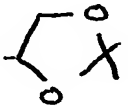
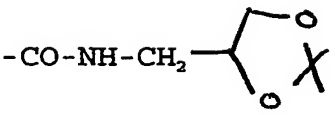
Particularly preferably, the organoiodine compound is a compound of formula I or II



(I)

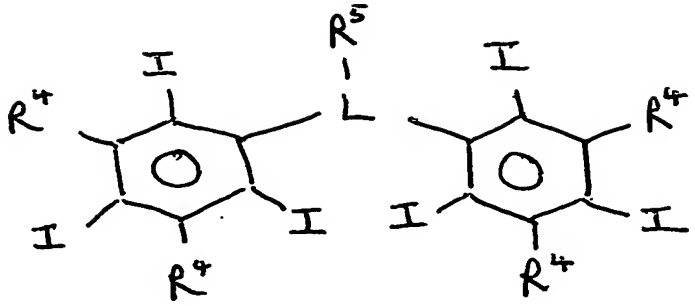


(II)

where Y is a group $-NHCOCH_3$,
$-CONH-CH_2CH(OCOCH_3)CH_2(OCOCH_3)$,
$-NHCOCH_2CH(OCOCH_3)CH_2(OCOCH_3)$, -NH-CO-  , -CO-NH-CH_2- 

$-NH-CO-C(CH_3)=CH_2$, $-NH-CO-NH-D-NH-CO-C(CH_3)=CH_2$,
$-NH-CH_2-CO-O-D-CO(CH_3)=CH_2$,
$-NH-CH_2-CO-NH-D-NH_2-CO-C(CH_3)=CH_2$,
$-CO-NH-D-NH-CO-C(CH_3)=CH_2$, or $-CO-O-D-O-CO-C(CH_3)=CH_2$,
i.e. a compound which is non-polymerizable but soluble in acrylic monomers or a compound which is polymerizable with acrylic monomers respectively.

As mentioned above, the organoiodine compound may be a bis-iodobenzene compound. Examples of such compounds include those of formula III



(III)

where R^4 is a lipophilic non-polymerizable group (e.g. a group $(R^1COO)_nX\ CONR^2$-, etc as defined above, in particular a group $-CONHCH_2CH(OCOCH_3)CH_2(OCOCH_3)$ or -CONH-CH_2- ), L is a linker group providing a 3 to 5, preferably 3, atom bridge between the phenyl rings, preferably a nitrogen attached bridge (e.g a -N-C-N- bridge), and R^5 is a polymerizable group, e.g. a (meth)acrylate or (meth)acrylamide (e.g. $CH_2=C(CH_3)COO$ or $CH_2=C(CH_3)CONH$) group optionally attached via a linker, e.g. a C_{1-6} alkanediyl group.

Alternative preferred non-polymerizable and polymerizable organoiodine compounds include analogs of known non-ionic, monomeric or dimeric organoiodine X-ray contrast agents in which solubilizing hydroxyl groups are acylated (e.g. acetylated) or formed into 2,4-dioxacyclopentan-1-yl groups and/or, where the compound is to be polymerizable, in which a carbonyl- or nitrogen-attached ring substituent is replaced by a (meth)acrylamide group or a (meth)acrylamidoalkylamino carbonyl group).

Examples of conventional non-ionic X-ray contrast agents which may be modified in this way include: iohexol, iopentol, iodixanol, iobitridol, iomeprol, iopamidol, iopromide, iotrolan, ioversol and ioxilan. The use of the analogs of the contrast agents with regulatory approval (eg in the US, Japan, Germany, Britain, France, Sweden or Italy) is preferred. The use of the analogs of the monomeric contrast agents is

particularly preferred. Such analogs may be prepared by acylation (e.g. acetylation) of the contrast agent itself or of an aminobenzene precursor and, where the analog is to be polymerized, by subsequent reaction of an optionally activated alkeneoic acid (e.g. an alkeneoic acid chloride (for example methacrylic acid chloride)) with an aminobenzene precursor. The preparation of such contrast agents and their aminobenzene precursors is widely described in the patent and scientific literature.

The use of such analogs is especially advantageous as any organoiodine compound released from the bone cement, e.g. due to esterase activity of biological fluids, will be in the form of a physiologically tolerable compound or a compound with biodistribution, bioelimination and biotolerability closely similar to the known and approved contrast agents. Before such exposure to esterase activity, the lipophilic acyl groups will moreover serve to reduce any leaching of the organoiodine compound from the bone cement.

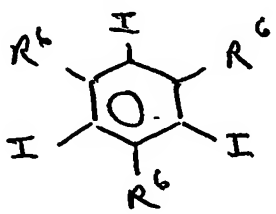
The organoiodine compound, i.e. a monomer and/or a monomer soluble compound, may constitute up to 100% wt of the liquid or particulate portion if a monomer but generally will constitute 2 to 75% wt, more preferably 5 to 50% wt, especially 10 to 25% wt of the portion(s) it is present in. Especially preferably it is present in both portions, and particularly at a weight percentage in the liquid portion which is within 5% wt, especially within 2% wt, of the weight percentage in the particulate portion.

If desired, some or all of the organoiodine compound may take the form of a cross-linking agent carrying at least two and optionally up to 10 or more polymerizable groups (e.g. (meth)acrylic groups). Generally however such cross-linking agents will constitute only a minor proportion, e.g. up to 20% (on a molar iodine basis) of the total organoiodine compound

used, more preferably up to 10%, especially up to 5%. Such cross-linking agents may conveniently be prepared by reacting conventional X-ray contrast agents of the types mentioned above or their aminobenzene precursors (or partly acylated versions of either thereof) with an optionally activated alkeneoic acid (e.g. methacrylic acid chloride).

Less preferably, the organoiodine compound may be an iodobenzene free from non-polymerizable lipophilic substituents (other than iodine of course), e.g. a simple iodobenzene (such as 1,4-diiodobenzene) or a simple iodoaminobenzene conjugate with (meth)acrylic acid (e.g. methacrylamido-2,4,6-triiodobenzene). Besides the organoiodine compound (where present), the liquid portion of the cement composition will comprise at least one polymerizable monomer, generally a monomer containing an ethylenically unsaturated bond, optionally a polymerization initiator, and optionally a cross-linking agent. The polymerization initiator and cross-linking agent may if desired be added to the liquid monomer or the liquid/particle mixture during preparation of the cement for use. Examples of suitable monomers include for example acrylic acid, methyl acrylate, ethyl acrylate, methacrylic acid, methyl methacrylate, butyl methacrylate and styrene. Especially preferably the monomer is methyl methacrylate, optionally together with butyl methacrylate, e.g. in a 4:1 to 10:1 ratio by weight, especially a 4.5:1 to 7:1 ratio.

Certain of the organoiodine compounds used according to the invention are themselves novel and form a further aspect of the invention. Thus viewed from this aspect the invention provides an organoiodine compound of formula IV



(IV)

wherein each R^6 group which may be the same or different, comprises an acyloxyalkylcarbonylamino, N-(acyloxyalkyl carbonyl)acyloxyalkylamino, N-acyloxyalkylcarbonyl-N-alkyl-amino, acyloxyalkylaminocarbonyl, bis(acyloxyalkyl)aminocarbonyl, N-acyloxyalkyl-N-alkyl-aminocarbonyl, alkoxyalkylaminocarbonyl, N-alkyl-alkoxyalkylaminocarbonyl, bis(alkoxyalkyl)amino-carbonyl, alkoxyalkylcarbonylamino, N-alkyl-alkoxyalkylcarbonylamino or N-alkoxyalkylcarbonyl-alkoxyalkylamino group or a triiodophenyl group attached via a 1 to 10 atom bridge (preferably composed of bridging atoms selected from O, N and C) optionally substituted by an acyloxyalkyl, acyloxyalkylcarbonyl, acyloxyalkylamino, acyloxyalkylcarbonylamino, acyloxyalkylaminocarbonyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxyalkylamino, alkoxyalkylcarbonylamino, or alkoxyalkylaminocarbonyl group or by a polymerizable group, e.g. a (meth)acrylate or (meth)acrylamide group, or one or two R^6 groups is/are a polymerizable group, e.g. a (meth)acrylate or (meth)acrylamide group, optionally attached via a 1 to 10 atom bridge, e.g. an alkylaminocarbonyl or alkylcarbonylamino bridge; or where one R^6 group is a polymerizable group, one or both of the remaining R^6 groups may be an alkylamino, bisalkylamino, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, alkylaminocarbonyl or bis-alkyl-aminocarbonyl group, (e.g. an acetylamino group). In such compounds, any alkyl or alkylene moiety preferably contains 1 to 6 carbon atoms, especially 2 to 4 carbon atoms and any bridge optionally comprises oxygen and/or nitrogen atoms, especially one or two nitrogen atoms. Moreover, two alkoxy groups in such compounds, especially groups attached to neighbouring carbon atoms, may be fused to form a cyclic bis-ether, preferably containing two ring oxygens and three ring carbons, e.g. as a 2,4-dioxa-3,3-dimethyl-cyclopentan-1-yl group. In general, it is

preferred that two R^6 groups are carbonyl-attached and that one is nitrogen-attached to the iodobenzene ring.

The compounds according to the invention may be prepared from triiodophenyl carboxylic acids and amines, e.g. conventional intermediates in X-ray contrast agent production, by protection of hydroxy groups and reaction of the carboxyl group (optionally after activation) or amino group with a polymerizable amine or carboxylic acid or activated carboxylic acid optionally subsequent to reaction with a spacer molecule, e.g. a diol or diamine.

The polymerization initiator, where present, is preferably a physiologically tolerable initiator of polymerization of ethyleneically unsaturated monomers, e.g. N,N-dimethyl-p-toluidine, N,N-dimethylaminobenzyl alcohol (DMOH) or N,N-dimethylaminobenzyl oleate (DMAO). This initiator is conveniently included as 0.1 to 5% wt of the liquid monomer composition, preferably 1 to 3% wt.

If a cross-linking agent (e.g. an organoiodine compound containing 2 or more polymerizable ethylenic bonds, divinylbenzene, ethyleneglycoldimethylacrylate, etc) is present in the liquid monomer composition, this is preferably as up to 2% wt of the composition, especially 0.1 to 1% wt of the composition.

If desired, the liquid monomer composition may also comprise an antibiotic compound, e.g. gentamicin, colistin, erythromycin, clindamicin, etc. Such antibiotics are included in several conventional bone cements and may be used in similar concentrations in the bone cement of the invention. Preferably however such an antibiotic is included in the form of a lipophilic ester, e.g. an acetyl ester, whereby to allow its release from the cement over a prolonged period as a result of esterase activity in the physiological fluids contacting the cement after prosthesis implantation. Alternatively, such antibiotics may be included

functionalized to incorporate a polymerizable ethylenically unsaturated bond coupled via an ester group to the antibiotic moiety, whereby again to release the antibiotic moiety over a prolonged period as a result of esterase activity. This use of antibiotic esters is novel and forms a further aspect of the invention.

As with conventional liquid monomer portions of bone cements, the portion may contain further components, e.g. hydroquinone, growth hormone, vitamins (e.g. vitamin D and vitamin E), etc.

The liquid monomer portion conveniently comprises 25 to 45% wt of the cement, especially preferably 30 to 35% wt.

The second component of the bone cement of the invention is a particulate polymer. This may be prepared by any conventional polymerization process, e.g. emulsion, suspension, liquid, slurry or gas phase polymerization, but is preferably prepared by emulsion polymerization or by the swelling and polymerization process pioneered by Prof. Ugelstad of NTSU, Norway (see the patent and scientific publications by Ugelstad and by Sintef/Sinvent).

The monomers and, where used, the organoiodine components and cross-linking agents, used in the preparation of the particulate polymer portion of the bone cement may be any of the materials described above in connection with the liquid monomer portion.

Particularly preferably, the monomer and, where present, the organoiodine compound used in the preparation of the particulate polymer portion are the same as are described above for use in the liquid monomer composition.

The polymerization initiator used in the preparation of the particulate polymer portion may be any compound suitable for polymerization initiation. Examples of suitable initiators include benzyl peroxide

(BPO), 2,2'-azo-bis-isobutyronitrile (AIBN) and tert. butyl peroxybenzoate. Preferably however benzoyl peroxide is used.

The relative concentrations of organoiodine compound and monomer used in the preparation of the particulate polymer portion are preferably as described above for the liquid monomer portion; especially preferably they are the same as in the liquid monomer portion.

The particulate polymer portion preferably has a mode particle size (i.e. maximum particle dimension in any direction) of 1 to 200 μm, particularly 2 to 100 μm, especially 10 to 70 μm; especially preferably the particulate is substantially monodisperse, e.g. with a coefficient of variation of less than 10%, especially less than 5%.

The particulate portion may, but generally will not, contain further components such as the antibiotics (in particular clindamycin), growth hormones, vitamins, etc mentioned above.

As with conventional bone cements, the cement composition of the invention should be mixed in a way that minimizes incorporation of gas bubbles into the set cement. Typically this will involve mixing the liquid and particulate portions under reduced pressure. However in a preferred embodiment mixing is effected in a helium atmosphere, especially preferably using portions that have been degassed and then helium flushed and if appropriate packed in a helium atmosphere. This use of helium in bone cement preparation is novel and forms a further aspect of the present invention. Viewed from this aspect the invention provides a method of producing a bone cement comprising admixing a liquid monomer portion and a particulate polymer portion, characterized in that admixture of said portions is effected under helium.

In a further aspect the invention provides a method

of affixing a joint prosthesis comprising inserting said prosthesis and a bone cement into a bone cavity, characterized in that said cement is a cement according to the invention.

The bone cements according to the invention are especially beneficial as compared to conventional zirconia-containing bone cements due to their X-ray opacity at the enhanced irradiation intensities necessary for investigation of joint prosthesis.

In a further aspect of the invention, in place of the organoiodine compounds, directly analogous organobromine compounds may be used. The resulting cements are especially useful as dental cements and as bone cements for thin extremities where lower X-ray voltages may be used.

The invention will now be described further with reference to the following non-limiting Examples. Parts and percentages are by weight unless otherwise indicated.

Example 1
Synthesis of iohexol-O-hexaacetate

Iohexol (24.63 g, 30.00 mmol) was suspended in a solution of acetic anhydride (100 ml) and pyridine (20 ml). The mixture was stirred for 24 hours at ambient temperature and then evaporated *in vacuo*, diluted with CH_2Cl_2 (200 ml) and washed with 0.1 M HCl (3 x 50 ml). The organic layer was dried with anhydrous $MgSO_4$, filtered and evaporated *in vacuo* producing a white crystalline solid (28.23 g, 87.67%).

^{1}H NMR	6.88-6.77 (m, 1 H), 5.31-5.20 (m, 3 H), 4.39-3.56 (m, 12 H), 2.06-2.00 (m, 18 H), 1.86 (d, 3 H)
MS(ES)	1095.9 ($M+Na^+$, 100)

Example 2

Synthesis of iodixanol-O-nonaacetate

Iodixanol (4.65 g, 3.00 mmol) was suspended in a solution of acetic anhydride (20 ml) and pyridine (4 ml). The reaction mixture was stirred for 24 hours and then evaporated *in vacuo*, diluted with CH_2Cl_2 (40 ml) and washed with 0.1 M HCl (3 x 25 ml). The organic layer was dried with anhydrous $MgSO_4$, filtered and evaporated *in vacuo* producing a white crystalline solid (5.27 g, 91.1%).

^{1}H NMR 6.66-6.44 (m, 4 H), 5.19 (br s, 5 H), 4.37-3.50 (m, 20 H), 2.04 (s, 18 H), 1.86-1.72 (m, 9 H), 1.21 (s, 6 H)

MS(ES) 1950.8 ($M+Na^+$, 100), 439.2 (18)

Example 3

Polymerization of MMA to form PMMA particles containing 10% iohexol-hexaacetate

A solution of 0.5% polyvinylalcohol in water (300 ml) was heated to 80°C and the solution was "bubbled" with argon/nitrogen. A solution of methylmethacrylate (44.75 g), iohexol-hexaacetate (5.0 g) (from Example 1) and benzoylperoxide (0.25 g) was added dropwise to the solution over a period of 30-60 minutes. The polymerization mixture was refluxed for 2 days, cooled to ambient temperature and filtered. The solid was dried overnight at 60°C (44.5 g).

Example 4
Polymerization of MMA to form PMMA particles containing 6.67% iohexol-hexaacetate

A solution of 0.5% polyvinylalcohol in water (300 ml) was heated to 80°C and the solution "bubbled" with argon/nitrogen. A solution of methylmethacrylate (46.41 g), iohexol-hexaacetate (3.33 g) (from Example 1) and benzoylperoxide (0.25 g) was added dropwise to the solution over a period of 30-60 minutes. The polymerization mixture was refluxed for 2 days, cooled to ambient temperature and filtered. The solid was dried overnight at 60°C (43.9 g).

Example 5
Polymerization of MMA to form PMMA particles

A solution of 0.5% polyvinylalcohol in water (300 ml) was heated to 80°C and the solution "bubbled" with argon/nitrogen. A solution of methylmethacrylate (49.75 g) and benzoylperoxide (0.25 g) was added dropwise to the solution over a period of 30-60 minutes. The polymerization mixture was refluxed for 2 days, cooled to ambient temperature and filtered. The solid was dried overnight at 60°C (45.6 g).

Example 6
Polymerization of MMA to form PMMA particles containing 10% iodixanol-nonaacetate

A solution of 0.5% polyvinylalcohol in water (100 ml) was heated to 80°C and bubbled with argon/nitrogen. Iodixanol-nonaacetate (1 g) (from Example 2) was mixed with methylmethacrylate (9 g) under ultrasonic radiation, benzoylperoxide (50 mg) was added and the

resultant mixture was added dropwise to the solution over a period of 30-60 minutes. This polymerization mixture was refluxed for 2 days, cooled to ambient temperature and filtered. The solid product was dried overnight at 60°C (7.58 g).

Example 7
Preparation of bone cement comprising iohexol-hexaacetate in non-homogeneous phase (6.67% in final bone cement)

Prepolymerized particles of iohexol-containing polymethacrylate (PMMA) (40 g) (from Example 3) were mixed with a solution of methacrylate (18.4 g), N,N-dimethyl-p-toluidine (400 mg), hydroquinone (1.2 mg) and chlorophyll (8.0 mg) under reduced pressure in a syringe. After mixing for 2-3 minutes, the mixture was ready for application.

Example 8
Preparation of bone cement comprising iohexol-hexaacetate in homogeneous phase (6.67% in final bone cement)

Prepolymerized particles of polymethylmethacrylate (PMMA) (40 g) (from Example 5) were mixed with a solution of methylmethacrylate (14.4 g), iohexol-hexaacetate (4.0 g) (from Example 1), N,N-dimethyl-p-toluidine (400 mg) hydroquinone (1.2 mg) and chlorophyll (8.0 mg) under reduced pressure in a syringe. After mixing for 2-3 minutes, the mixture was ready for application.

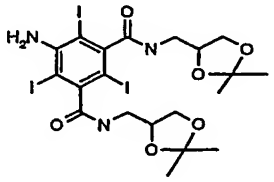
Example 9

Preparation of bone cement comprising iohexol-hexaacetate homogeneously distributed in the final cement (6.67% in final bone cement)

Prepolymerized particles of iohexol-containing polymethylmethacrylate (PMMA) (40 g) (from Example 4) were mixed with a solution of methylmethacrylate (17. 1 g), iohexol-hexaacetate (1.33 g) (from Example 1), N,N-dimethyl-p-toluidine (400 mg) hydroquinone (1.2 mg) and chlorophyll (8.0 mg) under reduced pressure in a syringe. After mixing for 2-3 minutes, the mixture was ready for application.

Example 10

Synthesis of 5-amino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide bis-acetonoid



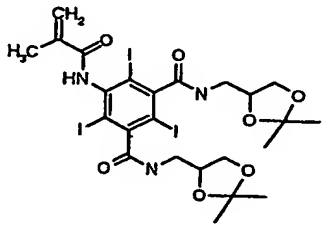
5-Amino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide (10.00 g, 14.18 mmol) (an intermediate in the preparation of iohexol) and toluene sulphonic acid (TsOH) (0.10 g, 0.52 mmol) were added to 2,2-dimethoxypropane (30 ml). The suspension mixture was stirred at ambient temperature for 48 hours and the ethanol formed was distilled off. The reaction mixture was evaporated in vacuo to yield a white solid (R_F=0.45 ethyl acetate).

^{1}H-NMR (DMSO): 8.70-8.64 (m, 2H), 4.24-4.20 (m, 2H), 4.05

(t, 2H), 3.83-3.77 (m, 2H), 3.43-3.16 (m, 4H), 1.34 (s,6H), 1.26 (s, 6H).

Example 11

Synthesis of 5-(propen-2-yl-carbonylamino)-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide bis-acetonoid

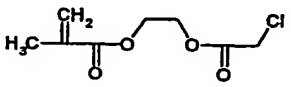


To the acetonoid product of Example 10 (1.57 g, 2.00 mmol) in ethylacetate (25 ml) and pyridine (1 ml) was added methacryloyl chloride (0.21 g, 2.00 mmol). The mixture was stirred at ambient temperature for 12 hours. The reaction mixture was added to ethylacetate (35 ml) and washed with water (3x15 ml). The organic layer was dried with $MgSO_4$, filtered and evaporated in vacuo to yield a white crystalline solid.

^{1}H-NMR (DMSO): 8.70-8.64 (m, 2H), 6.23 (s, 1H), 6.07 (s, 1H), 4.24-4.20 (m, 2H), 4.05 (t, 2H), 3.83-3.77 (m, 2H), 3.43-3.16 (m, 4H), 1.87 (s, 3H), 1.34 (s,6H), 1.26 (s, 6H).

Example 12

Synthesis of the chloroacetate ester of 2-hydroxy-methylmethacrylate



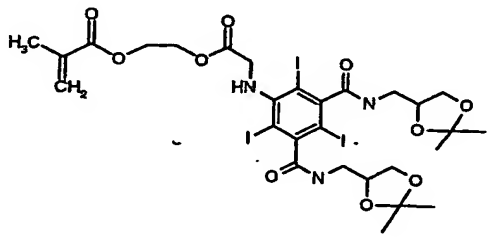
Chloroacetoylchloride (2.25 g, 20.00 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of hydroxyethyl methylmethacrylate (HEMA) (2.60 g, 20.00 mmol) and $N(C_2H_5)_3$ (2.02 g, 20.00 mmol) in CH_2Cl_2 (20 ml) at 0°C and stirred at ambient temperature overnight. The reaction mixture was added to CH_2Cl_2 (20 ml) and the mixture was washed with saturated $NaHCO_3$ (2x25 ml) and 1M HCl (25 ml), dried with $MgSO_4$, filtered and evaporated in vacuo to yield a yellow oil.

^{1}H-NMR ($CDCl_3$): 6.05 (2, 1H), 5.54 (s, 1H), 4.39-4.29 (m, 4H), 4.02 (s, 2H), 1.87 (s, 3H)

^{13}C-NMR ($CDCl_3$): 167.04, 166.87, 135.63, 126.10, 63.59, 61.85, 40.54, 18.05.

Example 13

Synthesis of 5-(propen-2-ylcarbonyloxyethyloxycarbonyl-methylamino)-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide bis-acetonoid

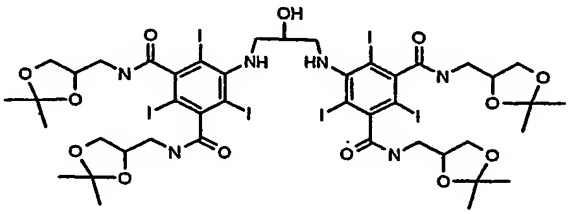


The compound of Example 12 (0.41 g, 2.00 mmol) in tetrahydrofuran (THF) was added dropwise to a solution of the acetonoid of Example 10 (1.57 g, 2.00 mmol) and $N(C_2H_5)_3$ (0.20 g, 2.00 mmol) in THF (20 ml). The mixture was stirred at ambient temperature for 24 hours. The reaction mixture was then evaporated down in vacuo, ethylacetate (30 ml) and H_2O (20 ml) were added and the mixture was transferred to a separation funnel. The aqueous layer was repeatedly extracted with ethylacetate (2x25 ml), dried with $MgSO_4$, filtered and evaporated in vacuo to yield a white crystalline powder.

^{1}H-NMR ($CDCl_3$): 7.24 (d, 2H), 6.06 (s, 1H), 5.54 (s, 1H), 4.39-4.32 (m, 6H), 4.06-4.01 (m, 4H), 3.78-3.43 (m, 6H), 1.79 (s, 3H), 1.36 (s, 6H), 1.23 (s, 6H).

Example 14

Synthesis of triiodophenyl dimer

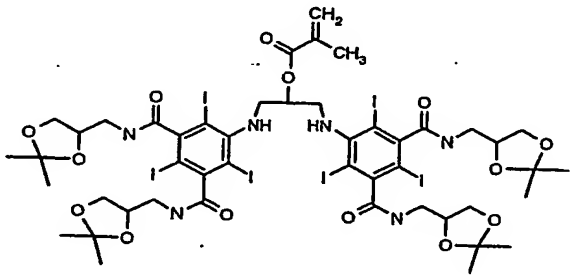


The acetonoid of Example 10 (3.14 g, 4.00 mmol) and K_2CO_3 (2.21 g, 16.00 mmol) in acetonitrile (40 ml) were added to 1,3-dibromo-2-propanol (0.44 g, 2.00 mmol) and the mixture was heated at 100°C for 24 hours, cooled to ambient temperature and filtered. The filtrate was evaporated in vacuo to yield a white crystalline solid.

^{1}H-NMR (DMSO): 8.71-8.57 (m, 4H), 5.48 (m, 1H), 4.30-4.23 (m, 4H), 4.10 (t, 4H), 3.87-3.79 (m, 4H), 3.40-3.23 (m, 12H), 1.38 (s, 12H), 1.29 (s, 12H)

Example 15

Synthesis of triiodophenyl dimer derivative



To the triiodophenyl dimer of Example 14 (1.62 g, 1.00 mmol) and $N(C_2H_5)_3$ (0.12 g, 1.2 mmol) in acetonitrile (15 ml) was added methacryloyl chloride (0.19 g, 1.2 mmol) in acetonitrile (5 ml). The mixture was stirred at ambient temperature for 12 hours. The mixture was then evaporated down in vacuo, ethylacetate (30 ml) was added and the resultant mixture was washed with H_2O (3x20 ml), dried with $MgSO_4$, filtered and evaporated in vacuo to yield a yellow crystalline solid.

^{1}H-NMR (DMSO): 8.71-8.45 (m, 4H), 6.23 (s, 1H), 6.01 (s, 1H), 5.45 (m, 1H), 4.25-4.21 (m, 4H), 4.05 (t, 4H), 3.82-3.77 (m, 4H), 3.56-3.18 (m, 12H), 1.93 (s, 3H), 1.34 (s, 12H), 1.25 (s, 12H)

Example 16

Synthesis of PMMA particles containing an iohexol-derivative

A solution of 0.5% polyvinylalcohol in water (100 ml) was heated to 80°C and bubbled with argon/nitrogen. The polymerizable acetonoid of Example 13 (0.477 g, 0.5 mmol) was mixed with methylmethacrylate (9.47 g, 94.6 mmol) under ultrasonic radiation, benzoylperoxide (50 mg) was added and the mixture was added dropwise to the solution over a period of 30-60 minutes. The polymerization mixture was refluxed for 2 days, cooled to ambient temperature and centrifuged at 4000 rpm for 10 minutes. The supernatant was removed, and the centrifugate was washed with water. The product was dried at 50°C to yield a white solid.

Example 17

Synthesis of PMMA particles containing an iohexol dimer

A solution of 0.5% polyvinylalcohol in water (100 ml) was heated to 80°C and bubbled with argon/nitrogen. The polymerizable dimer of Example 15 (0.87 g, 0.5 mmol) was mixed with methylmethacrylate (9.07 g, 90.6 mmol) under ultrasonic radiation, benzoylperoxide (50 mg) was added and the mixture was added dropwise to the solution over a period of 30-60 minutes. The polymerization mixture was refluxed for 2 days, cooled to ambient temperature and centrifuged at 4000 rpm for 10 minutes. The supernatant was removed, and the centrifugate was washed with water. The product was dried at 50°C to yield a white solid.

Example 18
Synthesis of polymerizable amide derivative with spacer

Diatrizoic acid is reacted with oxalyl chloride (1 equivalent) in dimethylformamide (DMF) to form the corresponding acid chloride. The acid chloride is then further reacted with ethylenediamine to form the corresponding monoamide. The monoamide is then reacted with methacrylic acid chloride and the resulting amide acryl derivative is isolated by chromatography.

Example 19
Preparation of bone cement comprising a polymerizable iodinated compound homogenously distributed in the final cement

Bone cement is prepared analogously to Example 9 using the PMMA particles of Example 16 and the polymerizable derivative of Example 15 in the MMA homogenous phase. The concentration of the compound of Example 16 in MMA is selected such that the concentration of iodine is approximately the same throughout the final polymer.

Example 20
Preparation of bone cement based on PMMA particles and a polymerizable amide

Bone cement is prepared analogously to Example 8 using the PMMA particles of Example 5 and 5% wt of the polymerizable compound of Example 11.

Example 21

Polymerization of MMA to form PMMA particles containing 5% ethyl-4-iodobenzoate

A solution of 0.5% polyvinylalcohol (PVA) in water (24 ml) was heated to 70°C and bubbled with argon/nitrogen. A solution of methylmethacrylate (3.78 g), ethyl-4-iodobenzoate (200 mg) and benzoylperoxide was added dropwise to the PVA solution over a period of 30-60 minutes. The polymerization mixture was refluxed for 3 days, cooled to ambient temperature and centrifuged at 4000 rpm for 10 minutes. The supernatant was removed, and the centrifugate was washed with water. The product was dried in vacuo at 50°C to a white solid.

Example 22

Polymerization of MMA to form PMMA particles containing 5% 1,2-diiodotetrafluorobenzene

A solution of 0.5% polyvinylalcohol (PVA) in water (24 ml) was heated to 70°C and bubbled with argon/nitrogen. A solution of methylmethacrylate (3.78 g), 1,2-diiodotetrafluorobenzene (200 mg) and benzoylperoxide (20 mg) was added dropwise to the PVA solution over a period of 30-60 minutes. The polymerization mixture was refluxed for 3 days, cooled to ambient temperature and centrifuged at 4000 rpm for 10 minutes. The supernatant was removed, and the centrifugate was washed with water. The product was dried in vacuo at 50°C to a white solid.

Example 23

Polymerization of MMA to form PMMA particles containing 10% iohexol-hexaacetate

A solution of 0.5% polyvinylalcohol (PVA) in water (300

ml) was heated to 70°C and bubbled with argon/nitrogen. A solution of methylmethacrylate (11.88 g), iohexol-hexaacetate (Example 1) (1.25 g) and benzoylperoxide (63 mg) was added dropwise to the PVA solution over a period of 30-60 minutes. The reaction mixture was stirred using a sonicator (ULTRA-TURRAX T 25 basic) at 11000 rpm. The polymerization mixture was refluxed for 3 days, cooled to ambient temperature and centrifuged at 4000 rpm for 10 minutes. The supernatant was removed, and the centrifugate was washed with water. The product was dried in vacuo at 50°C to a white solid. The particle size of the product was much lower than that of Example 3.

Example 24
Synthesis of PMMA particles containing a polymerizable iohexol-derivative

A solution of 0.5% polyvinylalcohol in water (100 ml) is heated to 80°C and bubbled with argon/nitrogen. The polymerizable iohexol derivative of Example 11 (0.477 g) is mixed with methylmethacrylate (9.47 g) under ultrasonic radiation, benzoylperoxide (50 mg) is added and the mixture is added dropwise to the PVA solution over a period of 30-60 minutes. The polymerization mixture is refluxed for 2 days, cooled to ambient temperature and filtered.

Example 25
Synthesis of PMMA particles containing a polymerizable iohexol-dimer

A solution of 0.5% polyvinylalcohol in water (100 ml) is heated to 80°C and bubbled with argon/nitrogen. The polymerizable dimer of Example 15 (0.87 g) is mixed with

methylmethacrylate (9.07 g) under ultrasonic radiation, benzoylperoxide (50 mg) is added and the mixture is added dropwise to the PVA solution over a period of 30-60 minutes. The polymerization mixture is refluxed for 2 days, cooled to ambient temperature and filtered.

Claims:

1. A bone cement comprising in admixture a monomer-containing liquid portion and a particulate polymer portion, characterized in that at least one of said portions comprises a dissolved non-polymerizable organoiodine compound.

2. A bone cement kit comprising a monomer-containing liquid portion and separate therefrom a particulate polymer portion, wherein at least one of said portions comprises a dissolved non-polymerizable organoiodine compound, said kit optionally and preferably further comprising instructions for the preparation of a bone cement therewith.

3. A bone cement comprising in admixture a monomer-containing liquid portion and a particulate polymer portion, characterized in that said liquid portion comprises a polymerizable organoiodine compound and the polymeric structure of said particulate polymer comprises covalently bonded residues of a polymerizable organoiodine compound.

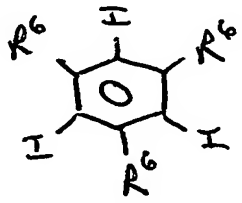
4. A bone cement kit comprising a monomer-containing liquid portion and separate therefrom a particulate polymer portion, wherein said liquid portion comprises a polymerizable organoiodine compound and the polymeric structure of said particulate polymer comprises covalently bonded residues of a polymerizable organoiodine compound, said kit optionally and preferably further comprising instructions for the preparation of a bone cement therewith.

5. A bone cement comprising in admixture a monomer-containing liquid portion and a particulate polymer portion, characterized in that said liquid portion

comprises a polymerizable organoiodine compound and/or the polymeric structure of said particulate polymer comprises covalently bonded residues of a polymerizable organoiodine compound, wherein said polymerizable organoiodine compound comprises an organoiodine moiety covalently bonded via an amide but not an ester bond to a polymerizable moiety.

6. A bone cement kit comprising a monomer-containing liquid portion and separate therefrom a particulate polymer portion, wherein said liquid portion comprises a polymerizable organoiodine compound and/or the polymeric structure of said particulate polymer comprises covalently bonded residues of a polymerizable organoiodine compound, wherein said polymerizable organoiodine compound comprises an organoiodine moiety covalently bonded via an amide but not an ester bond to a polymerizable moiety.

7. An organoiodine compound of formula IV



(IV)

wherein each R^6 group which may be the same or different, comprises an acyloxyalkylcarbonylamino, N-(acyloxyalkyl carbonyl)acyloxyalkylamino, N-acyloxyalkylcarbonyl-N-alkyl-amino, acyloxyalkylaminocarbonyl, bis(acyloxyalkyl)aminocarbonyl, N-acyloxyalkyl-N-alkyl-aminocarbonyl, alkoxyalkylaminocarbonyl, N-alkyl-alkoxyalkylaminocarbonyl, bis(alkoxyalkyl)amino-carbonyl, alkoxyalkylcarbonylamino, N-alkyl-alkoxyalkylcarbonylamino or N-alkoxyalkylcarbonyl-alkoxyalkylamino group or a triiodophenyl group attached via a 1 to 10 atom bridge (preferably composed of bridging atoms selected from O, N and C) optionally

substituted by an acyloxyalkyl, acyloxyalkylcarbonyl, acyloxyalkylamino, acyloxyalkylcarbonylamino, acyloxyalkylaminocarbonyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxyalkylamino, alkoxyalkylcarbonylamino, or alkoxyalkylaminocarbonyl group or by a polymerizable group, e.g. a (meth)acrylate or (meth)acrylamide group, or one or two R^6 groups is/are a polymerizable group, e.g. a (meth)acrylate or (meth)acrylamide group, optionally attached via a 1 to 10 atom bridge, e.g. an alkylaminocarbonyl or alkylcarbonylamino bridge; or where one R^6 group is a polymerizable group, one or both of the remaining R^6 groups may be an alkylamino, bisalkylamino, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, alkylaminocarbonyl or bis-alkyl-aminocarbonyl group, (e.g. an acetylamino group).

8. A method of producing a bone cement comprising admixing a liquid monomer portion and a particulate polymer portion, characterized in that admixture of said portions is effected under helium.

9. A method of affixing a joint prosthesis comprising inserting said prosthesis and a bone cement into a bone cavity, characterized in that said cement is a cement as claimed in any one of claims 1, 3 and 5.